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Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings

Kempf, Werner ; Kazakov, Dmitry V ; Baumgartner, Hans-Peter ; Kutzner, Heinz

Abstract: **BACKGROUND:** Follicular lymphomatoid papulosis (LyP) describes a variant of LyP with perifollicular infiltrates and some degree of folliculotropism of CD30(+) atypical lymphocytes. So far, only a few cases of follicular LyP have been described. **OBJECTIVE:** Our goal was to study the clinicopathologic features of follicular LyP in a series of 11 cases (9 male, 2 female; age range 7-78 years, mean age 50 years). **METHODS:** In all, 113 cases of LyP were reviewed to select cases showing follicular involvement. Histology was correlated with the clinical data to exclude cases of CD30(+) anaplastic large-cell lymphoma or folliculotropic mycosis fungoides. **RESULTS:** Six cases were classified as type C and 4 as type A, whereas the remaining case manifested epidermotropism of small lymphocytes in a background of a typical type A lesion (overlapping type A/B). Perifollicular infiltrates of CD30(+) atypical lymphoid cells were seen in all 11 cases, with infiltration of the follicular epithelium in 8 cases. Hyperplasia of the follicular epithelium was observed in 4 cases; ruptured hair follicles, in 3 cases; and follicular mucinosis, in 2 cases. In addition to hair follicle infiltration, atypical cells were recognized within sebaceous glands in 2 lesions. New findings were presence of numerous intrafollicular neutrophils in 2 patients, who clinically had pustules in addition to papules. Other histopathological features encountered included perieccrine infiltration (n = 5), focal subcutaneous involvement (n = 4), granulomatous inflammation (n = 3), epidermal hyperplasia (n = 2), and 1 each of infiltration of muscle bundles, numerous eosinophils in the infiltrate, and angiocentricity. **LIMITATIONS:** This was a retrospective study. **CONCLUSIONS:** Follicular LyP is a variant of LyP with involvement of hair follicles, mostly in the form of perifollicular infiltrate with variable degree of folliculotropism. Other changes including hyperplasia of the follicular epithelium, rupture of hair follicle, and follicular mucinosis are less common. Rarely, intrafollicular pustules can be seen in the follicular epithelium; such lesions manifest clinically as pustules.

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Abstract: Background: The term follicular lymphomatoid papulosis (LyP) is applied to a variant of LyP with perifollicular distribution of the infiltrate and some degree of folliculotropism of CD30+ atypical lymphocytes.

Objective: Our goal was to study prevalence and clinico-pathologic features of follicular LyP in a series of 11 cases (9 male; 2 female; age range 7-78 years; mean 50 years) .

Material and Methods: 113 cases of LyP were reviewed to select cases showing follicular involvement. Results: Perifollicular infiltrates of CD30+ atypical lymphoid cells were seen in all 11 cases, with infiltration of the follicular epithelium in 8 cases. Hyperplasia of the follicular epithelium was observed in 4 cases and ruptured hair follicles were present in 3 biopsy specimens. Follicular mucinosis was noted in 2 cases. In addition to hair follicle infiltration, atypical cells were recognized with sebaceous glands in 2 lesions. New findings were presence of intrafollicular neutrophils in 2 patients, who clinically also manifested pustular eruptions in addition to papules.

Limitations: This was largely a retrospective study of a well-known entity, therefore follow-up was not sought.

Conclusions: Follicular LyP is a variant of LyP with involvement of hair follicles, mostly in the form of perifollicular infiltrate with variable degree of folliculotropism. Other changes including hyperplasia of the follicular epithelium, rupture of hair follicle, follicular mucinosis are less common. Rarely, intrafollicular pustules (neutrophils collections) can be seen in the follicular epithelium and such lesions manifest themselves as pustules clinically.

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Manuscript submission

Dear Editors,

Enclosed please find our manuscript entitled "Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings" in which we report the largest series of this rare condition, including new histopathological findings.

We have now corrected the checklist as required.

Thank you very much for the evaluation of our manuscript.

Sincerely yours,

Werner Kempf,

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Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings

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The authors have no conflicts of interests to declare

Word count: 1383, References: 35, Tables: 1, Figures: 8

Lymphomatoid papulosis may present with unusual clinical and histological findings.

We present 11 cases of follicular lymphomatoid papulosis representing the largest series in the literature.

Histology is characterized by perifollicular infiltrates of CD30+ atypical lymphoid cells with variable degree of folliculotropism, follicular mucinosis and neutrophils in the follicle. The follicular variant may manifest with pustules as an unusual and diagnostically misleading clinical presentation of lymphomatoid papulosis.

Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings

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Abstract

Background: The term follicular lymphomatoid papulosis (LyP) is applied to a variant of LyP with perifollicular distribution of the infiltrate and some degree of folliculotropism of CD30+ atypical lymphocytes. Other alterations rarely reported in follicular LyP include cystic dilatation of a hair follicle, rupture of a hair follicle, hyperplasia of the follicular epithelium, and follicular mucinosis. To date, only few cases of follicular LyP have been described.

Objective: Our goal was to study prevalence and clinico-pathologic features of follicular LyP in a series of 11 cases (9 male; 2 female; age range 7-78 years; mean 50 years) .

Material and Methods: 113 cases of LyP were reviewed to select cases showing follicular involvement. Histology was correlated with the clinical data to exclude cases of CD30+ anaplastic large cell lymphoma or folliculotropic mycosis fungoides.

Results: Six cases were classified as type C and 4 as type A, whereas the remaining case manifested epidermotropism of small lymphocytes in a background of a typical type A lesion (“overlapping type A/B”). Perifollicular infiltrates of CD30+ atypical lymphoid cells were seen in all 11 cases, with infiltration of the follicular epithelium in 8 cases. Hyperplasia of the follicular epithelium was observed in 4 cases and ruptured hair follicles were present in 3 biopsy specimens. Follicular mucinosis was noted in 2 cases. In addition to hair follicle infiltration, atypical cells were recognized with sebaceous glands in 2 lesions. New findings were presence of intrafollicular neutrophils in 2 patients, who clinically also manifested pustular eruptions in addition to papules. Other histopathological features encountered included perieccrine infiltration (n=5), focal subcutaneous involvement (n=4), granulomatous inflammation (n=3), epidermal hyperplasia (n=2) and one each of infiltration of muscle bundles, numerous eosinophils in the infiltrate, and angiocentricity.

Limitations: This was a retrospective study.

Conclusions: Follicular LyP is a variant of LyP with involvement of hair follicles, mostly in the form of perifollicular infiltrate with variable degree of folliculotropism. Other changes

including hyperplasia of the follicular epithelium, rupture of hair follicle, follicular mucinosis are less common. Rarely, intrafollicular pustules (neutrophils collections) can be seen in the follicular epithelium and such lesions manifest themselves as pustules clinically.

Abbreviations

ALCL - anaplastic large cell lymphoma

LyP – lymphomatoid papulosis

Introduction

Several clinicopathological variants of lymphomatoid papulosis (LyP) have been delineated, sometimes occurring in the same individual. The commonest histopathological variants are LyP type A and C which are characterized by wedge-shaped or nodular infiltrates of large pleomorphic or anaplastic CD30+ lymphoid cells arranged as scattered atypical cells in the background of eosinophils and neutrophils (type A) or in cohesive sheets/nodules with more than 50% of atypical cells (type C) imitating CD30+anaplastic large cell lymphoma (ALCL). (1) Less common forms are LyP type B and the recently described type D, both showing an epidermotropic infiltrate of atypical lymphocytes with variable expression of CD30, which histopathologically resembles mycosis fungoides and cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, respectively. (2), (3) Cases with overlapping patterns have been reported. (1) Most recently, a new variant of LyP has been proposed, namely, type E characterized by a predominantly angioinvasive infiltrate and oligolesional presentation with eschar-type necrosis (4)

The term follicular lymphomatoid papulosis (LyP) was introduced in 1980 by Pierard, Ackerman and Lapiere who reported two patients with LyP with perifollicular distribution of the infiltrate. (5) Other changes related to hair follicles encountered in the biopsies from the above patients were cystic dilatation of a hair follicle (infundibular cyst), rupture of a hair follicle and hyperplasia of the follicular epithelium. (5) Since the original description, only few more cases under designation of follicular LyP have subsequently been described, mostly as isolated case reports, documenting, in addition to the above changes, rare instances of intrafollicular atypical cells (folliculotropism) and follicular mucinosis. (6), (7), (8), (9), (1), (10) Here we present the first series of follicular LyP which encompasses 11 cases and describe hitherto unreported features, namely neutrophils collections (pustules) in the follicular epithelium.

Material and Methods

After encountering 2 patients with folliculocentric LyP and neutrophils collections in the follicular epithelium as identified histopathologically, we retrospectively retrieved cases of CD30+lymphoproliferative disease from our files to identify cases with follicular involvement. A search was performed for cases displaying any of the following: perifollicular distribution of the infiltrate, intrafollicular CD30+ cells, cystic dilatation of a hair follicle, rupture of hair follicles, hyperplasia of the follicular epithelium, follicular mucinosis, and neutrophils collection in the follicular epithelium. The main clinical data (age, gender, location, clinical presentation, treatment and follow-up) were obtained from the medical charts and contributing clinicians and were correlated with histology to exclude cases of CD30+ ALCL and mycosis fungoides with expression of CD30. A total of 113 LyP cases were reviewed, and 11 cases of follicular LyP were found. For each case only one biopsy specimen was available for review. The cases were classified into types A, B, and C according to the current histopathological classification of LyP. (11), (12) In addition to the above changes related to hair follicles, we documented other alterations such as presence of granuloma, vessel involvement, adipose tissue involvement. In all the cases, immunohistochemical studies (CD30) had been performed prospectively at the time of diagnosis.

Results

Clinical findings

There were 9 male and 2 female patients ranging in age at time of diagnosis from 7 to 78 years (mean 50 years, median 59 years). All of them clinically presented with widespread recurrent papules and nodules, usually involving several anatomic sites in the course of the disease. In one patient the distribution of the lesions was confined to a certain anatomic site, i.e. face thus conforming to the concept of regional (localized) LyP (Figures 1, 2). (13) One patient had a history of Hodgkin disease. The detailed information is included in Table 1. Follow-up was available in two cases (cases 8 and 9). Both patients were alive with no evidence of disease at 40 and 26 months.

Histopathological findings

Of the 11 cases, 6 were classified as type C and 4 as type A. The remaining case manifested epidermotropism of small lymphocytes in a background of a typical type A lesion, thus matching the concept of so-called “overlapping type A/B”. (1) Perifollicular infiltrates of CD30+ atypical medium-sized to large lymphoid cells were seen in all 11 cases, whereas infiltration of the follicular epithelium in 8 cases and usually only few atypical lymphocytes were noted to invade the hair follicles (Figure 3). Hyperplasia of the follicular epithelium was observed in 4 cases and ruptured hair follicles were present in 3 biopsy specimens (Figures 4, 5). Follicular mucinosis was noted in two cases, and in one of them several hair follicles demonstrated mucin deposits (Figures 6, 7). In addition to hair follicle infiltration, atypical cells were recognized with sebaceous glands in 2 lesions. In 2 cases, there were neutrophils in the infundibula of the hair follicles, including the cornified layer and these patients clinically manifested, in addition to papulo-nodular lesions, pustules (Figures 1, 8). Other features encountered included perieccrine infiltration (n=5), focal subcutaneous involvement (n=5),

133 granulomatous inflammation (n=3), epidermal hyperplasia (n=2) and one each of infiltration
134 of muscle bundles, numerous eosinophils in the infiltrate, and angiocentricity.
135

Discussion

Our study shows that the follicular form accounts for 10% of LyP. This prevalence is slightly higher than the one reported in the study by that of El-Shabrawi, Kerl and Cerroni (5 out of 85; 5.8%). (1) The commonest alterations related to hair follicles in follicular LyP are a perifollicular infiltrate with mild degree of folliculotropism, whereas hyperplasia of the follicular epithelium, cystic dilatation of a hair follicle, its complete destruction and follicular mucinosis are rare features. These findings are in concert with the results of the few previously reported cases of follicular LyP. In two cases, neutrophils forming collections within the follicular epithelium were noted. Interestingly, these patients also manifested pustular eruptions in addition to papules and nodules. These features maybe diagnostically misleading and in fact the clinical diagnosis of acne and fungal infection was first considered in both patients. As far as we are aware, follicular pustules have not been previously reported in follicular LyP. In the patient reported by Kato et al pustules were seen clinically, but no intrafollicular neutrophils were mentioned on histology. (8)

In the previously published material and when specifically classified, types A, B, and C have been reported in follicular LyP. Folliculotropism was also noted in LyP, type E. (4). In our cohort, the most common type was type C. Pilosebaceous infiltration was overrepresented (8 out of 9 cases) in type C in a recent large series of LyP reported by de Souza et al. (14) Of note, the authors of the latter study identified an unusually high frequency of pilosebaceous infiltration in their series (68 out of 123 cases; 55.3%) compared to our study (11 out of 113; 9.7%).

We have detected some other features including subcutaneous involvement, granulomas, infiltration of muscle bundles, numerous eosinophils in the infiltrate, angiocentricity, and prominent epidermal hyperplasia. These have so far only rarely been reported in LyP. Some

of them such as infiltration of muscle bundles may impart a worrisome appearance to the lesion imitating a lymphoma but this feature has been described in pseudolymphomas and maybe anatomically site-related. (15), (16), (17) Angiocentricity is a feature of the above mentioned LyP type E and the cells permeating vessel wall usually show a cytotoxic phenotype. (4) In the case with numerous eosinophils, the latter widely outnumbered CD30 cells, similar to a situation in so-called neutrophil- or eosinophils-predominant ALCL. (18), (19), (20), (21), (22), (23), (24)

In summary, follicular LyP is a variation of LyP with involvement of hair follicle, mostly in the form of perifollicular infiltrate with some folliculotropism. Other changes including hyperplasia of the follicular epithelium, rupture of hair follicle, follicular mucinosis are less common. Rarely, intrafollicular pustules (neutrophil collections) can be seen in the follicular epithelium and such lesions clinically manifest themselves as pustules. This manifestation is clinically interpreted as folliculitis or acne as in our case with regional involvement on the face. Dermatologists and dermatopathologists should be aware of these unusual clinical and histological presentation of LyP. One could refer to follicular LyP as LyP, type F (follicular) to underscore follicular involvement, but we do not propose considering this variant a separate type of the disease in the sense of conventional histopathological classification. Keeping in mind that follicular involvement in LyP can sometimes be striking, the designation LyP, type F might however increase the alertness of the histopathologist and help in the differential diagnosis from other cutaneous lymphoproliferative conditions accompanied by follicular involvement, mostly mycosis fungoides and some pseudolymphomas. (25), (26), (27), (28), (29), (30), (31), (32), (33), (34), (35)

Figure legends

Figure 1. Folliculotropic lymphomatoid papulosis. Recurrent papulo-nodular lesions on the face (A, B, C). Apart from the face, the patient had similar lesions on the extremities (Case 8).

Figure 2. Folliculotropic lymphomatoid papulosis. In this patient, the lesions were localized to the face (so-called regional lymphomatoid papulosis) (A-D). Note pustular elements (A, C). Histopathologically, there is perifollicular infiltrate (F) composed of CD30 positive large cells (F). Note numerous neutrophils and debris in the cornified layer atop the infundibulum of the hair follicle (F) (Case 9).

Figure 3. Folliculotropic lymphomatoid papulosis. Perifollicular infiltrate with folliculotropism.

Figure 4. Folliculotropic lymphomatoid papulosis. Islands of hyperplastic follicular epithelium (A), with partial destruction (B).

Figure 5. Folliculotropic lymphomatoid papulosis. Hair follicle nearly completely destroyed by large anaplastic cells.

Figure 6. Folliculotropic lymphomatoid papulosis with subcutaneous involvement (A) and follicular mucinosis (B, C)

Figure 7. Folliculotropic lymphomatoid papulosis with folliculotropism, follicular mucinosis and mucinous degeneration of the sebaceous gland.

Figure 8. Folliculotropic lymphomatoid papulosis. Numerous neutrophils can be recognized in the infundibular epithelium (A, B). Note the surrounding CD30 positive atypical cells (Case 8).

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Table1. Follicular lymphomatoid papulosis: the main clinicopathological findings.

Case	Sex/Age	Site of biopsy	Clinical presentation/diagnosis	Histological Type	Histological changes related to hair follicle	Other histological changes
Case 1	F/61	Face	Face Lymphomatoid papulosis.	Type C	PF, IF, FM, HFE	Sebaceous gland infiltration, involvement of subcutis and muscle bundles
Case 2	M/7	Lower leg	One year history of multiple papules on the lower legs Lymphomatoid papulosis.	Type A/B	PF, IF	Granulomas
Case 3	M/27	Abdomen	Six months history of multiple nodules on the trunk.	Type A	PF, IF, HFE, RHF	Marked eosinophil predominance
Case 4	M/59	Limb	Two year history of multiple recurrent ulcerating papules on the trunk, buttock and extremities	Type C	PF	Epidermal hyperplasia, involvement of subcutis, perieccrine infiltration
Case 5	M/30	Limb	Eight month history of multiple recurrent nodules on the limbs. Lymphomatoid papulosis.	Type A	PF, IF	Angiocentricity, involvement of subcutis, perieccrine infiltration
Case 6	M/78	Elbow	Multiple nodules on the right elbow.	Type A	PF, IF	Sebaceous gland infiltration, involvement of subcutis, perieccrine infiltration , granulomas

Case 7	M/73	Abdomen	Five year history of recurrent papules with wide distribution, including genital area, trunk, limbs	Type C	PF	Perieccrine infiltration
Case 8	M/32	Face	Three year history of recurrent papules and nodules on the face and extremities.	Type A	PF, IFP	Epidermal hyperplasia
Case 9	M/55	Scalp	Two year history of papular and pustular lesions	Type C	PF, IF, IFP, HFE	
Case 10	F/67	Forehead	Recent history of Hodgkin disease (nodular sclerosis). Eruption of multiple nodules on the face and neck during chemotherapy for Hodgkin disease.	Type C	PF, RHF	Perieccrine infiltration
Case 11	M/65	Eyelid	Multiple lesions and one larger nodule	Type C	PF, IF, FM, HFE, RHF	Granulomas, involvement of subcutis

PF- perifollicular distribution of the infiltrate, IF – intrafollicular atypical cells HFE – hyperplasia of the follicular epithelium, RHF – rupture of a hair follicle, FM – follicular mucinosis

Figure 1
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Figure 2
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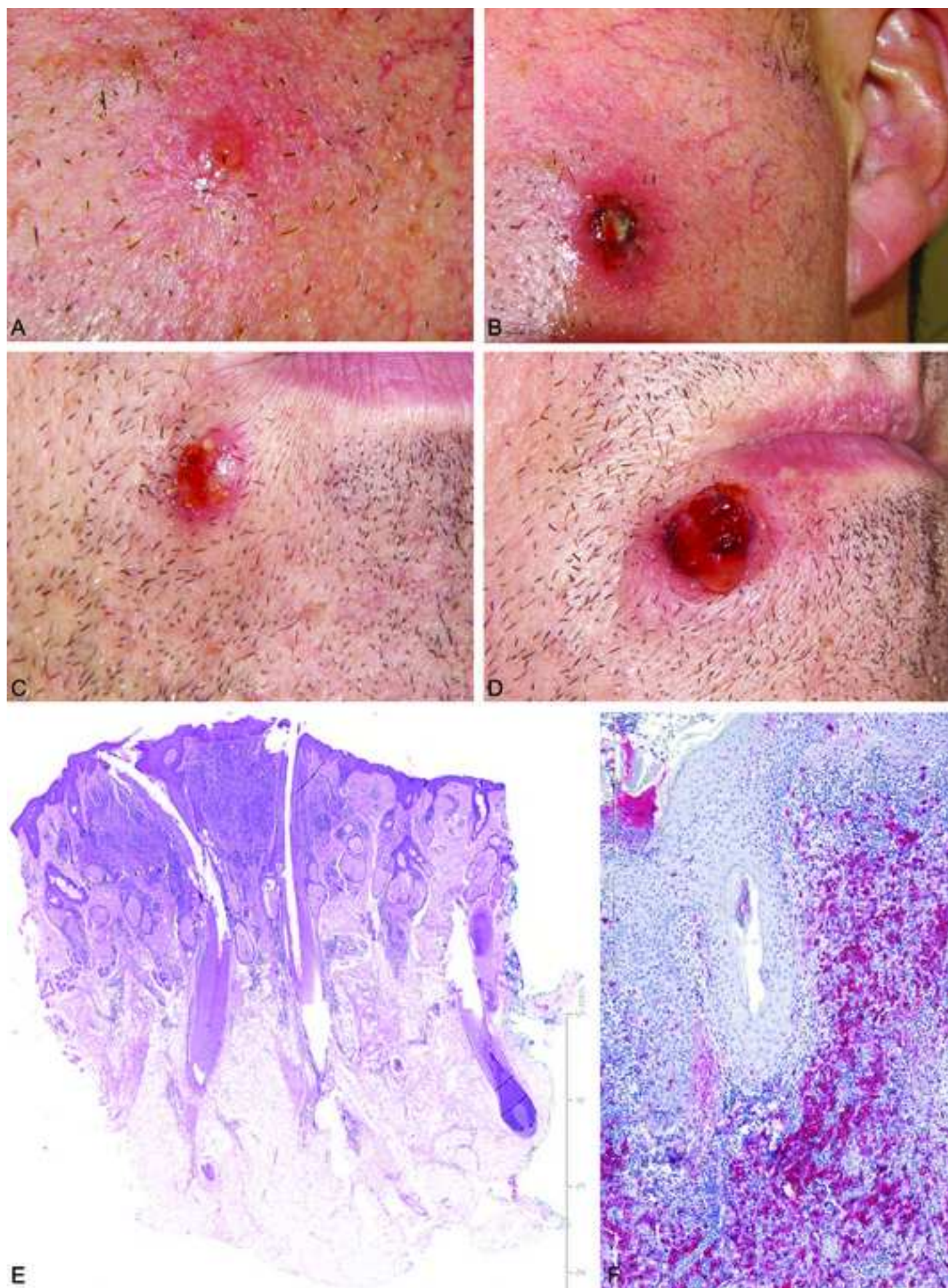


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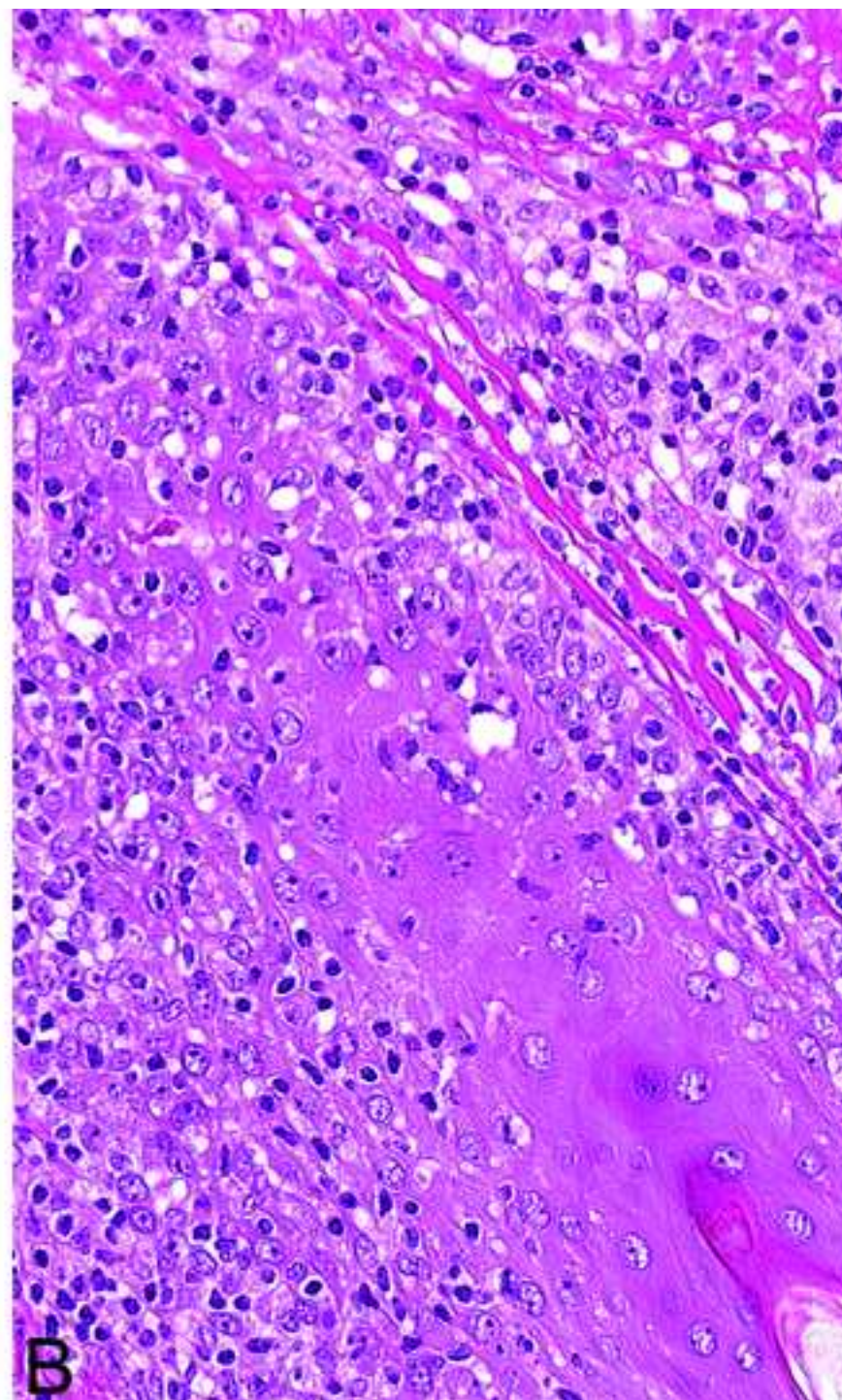
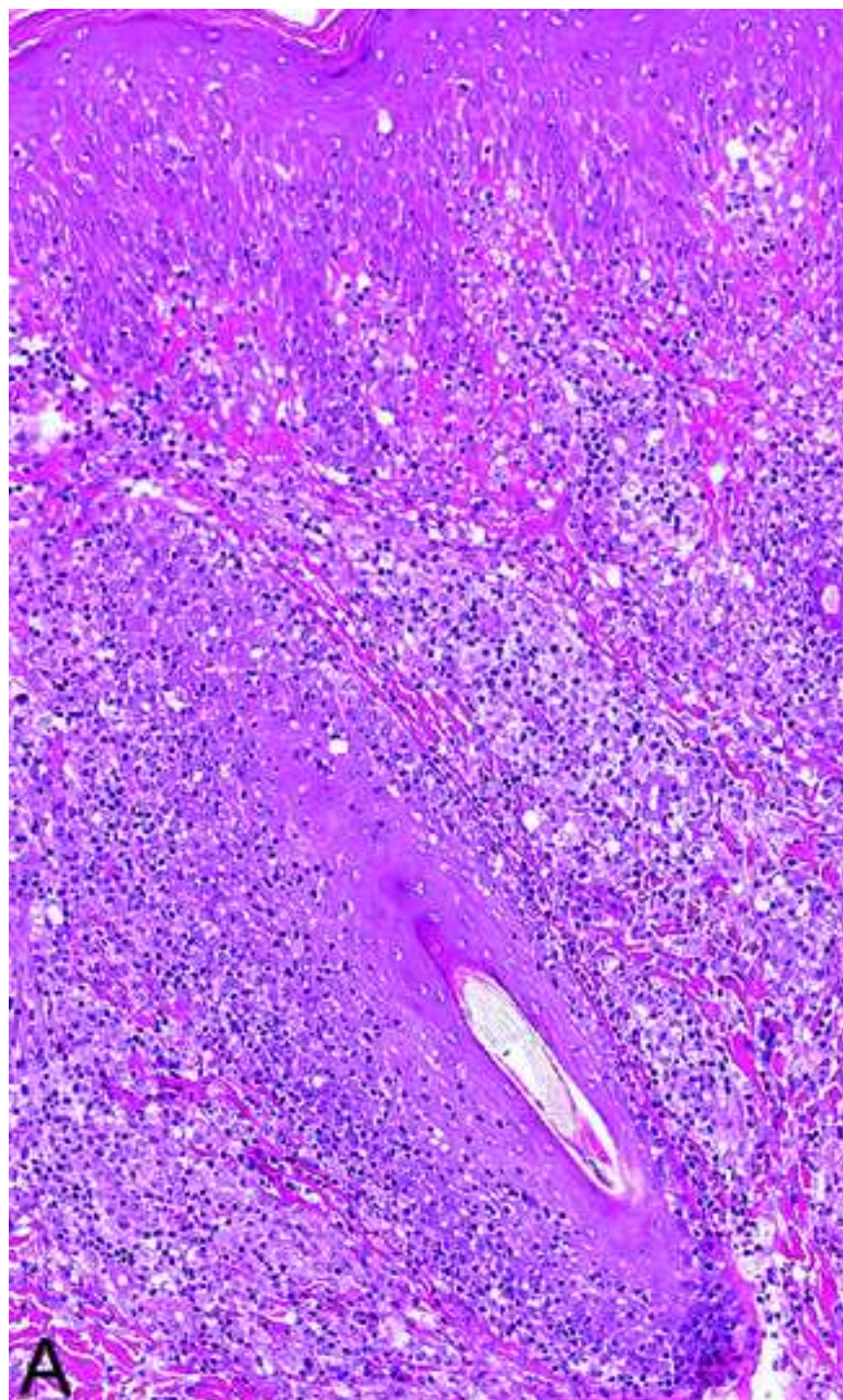


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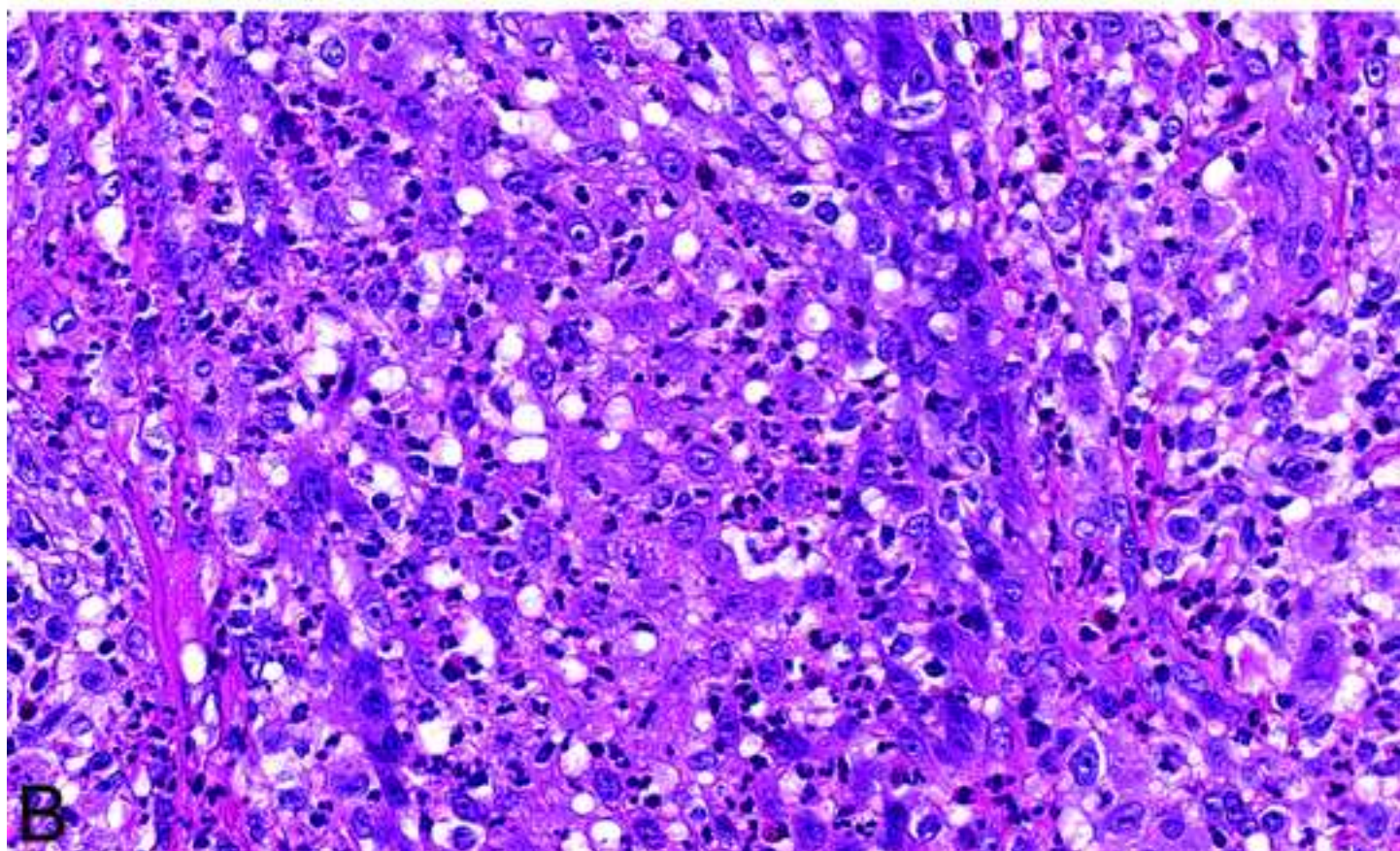
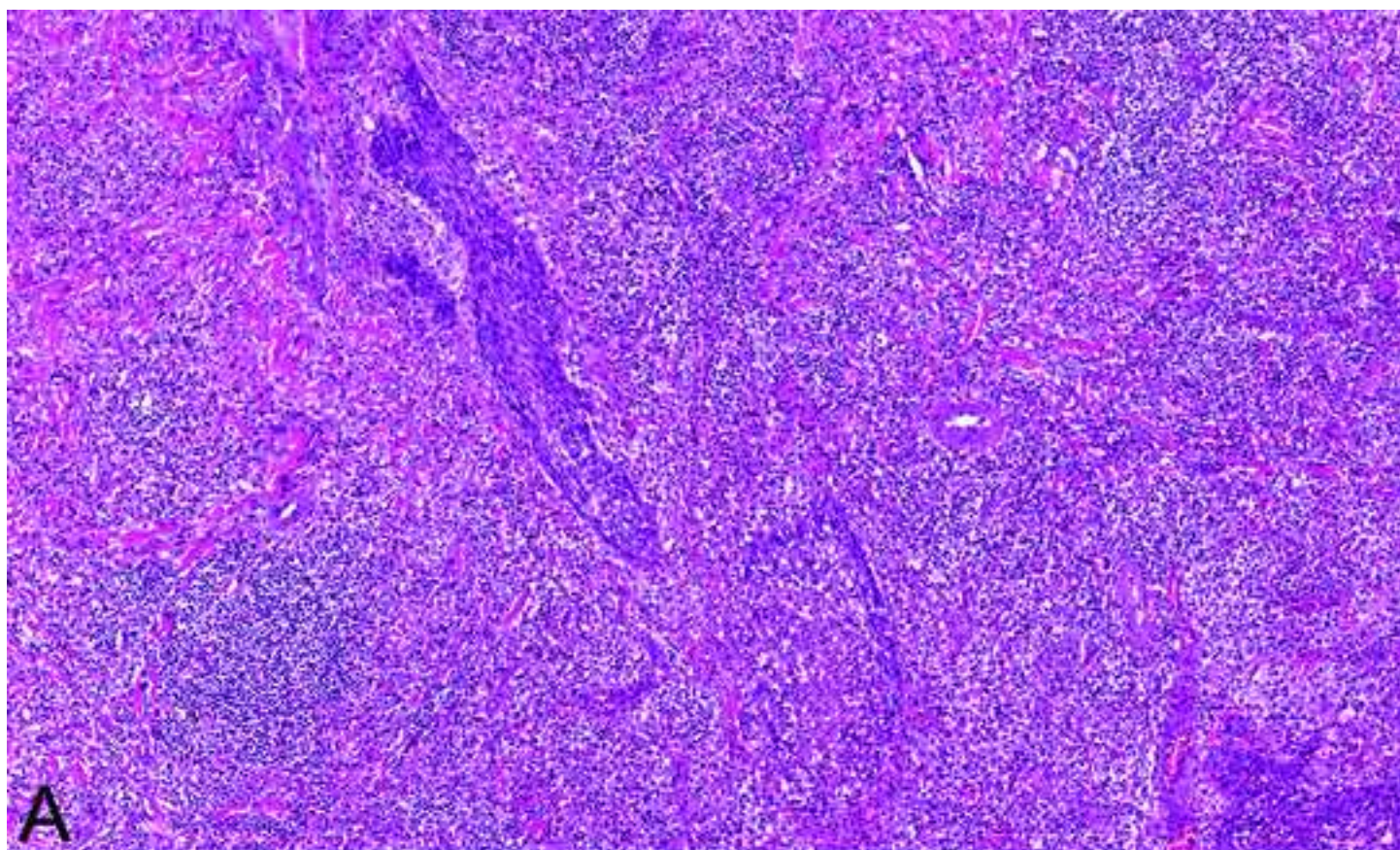


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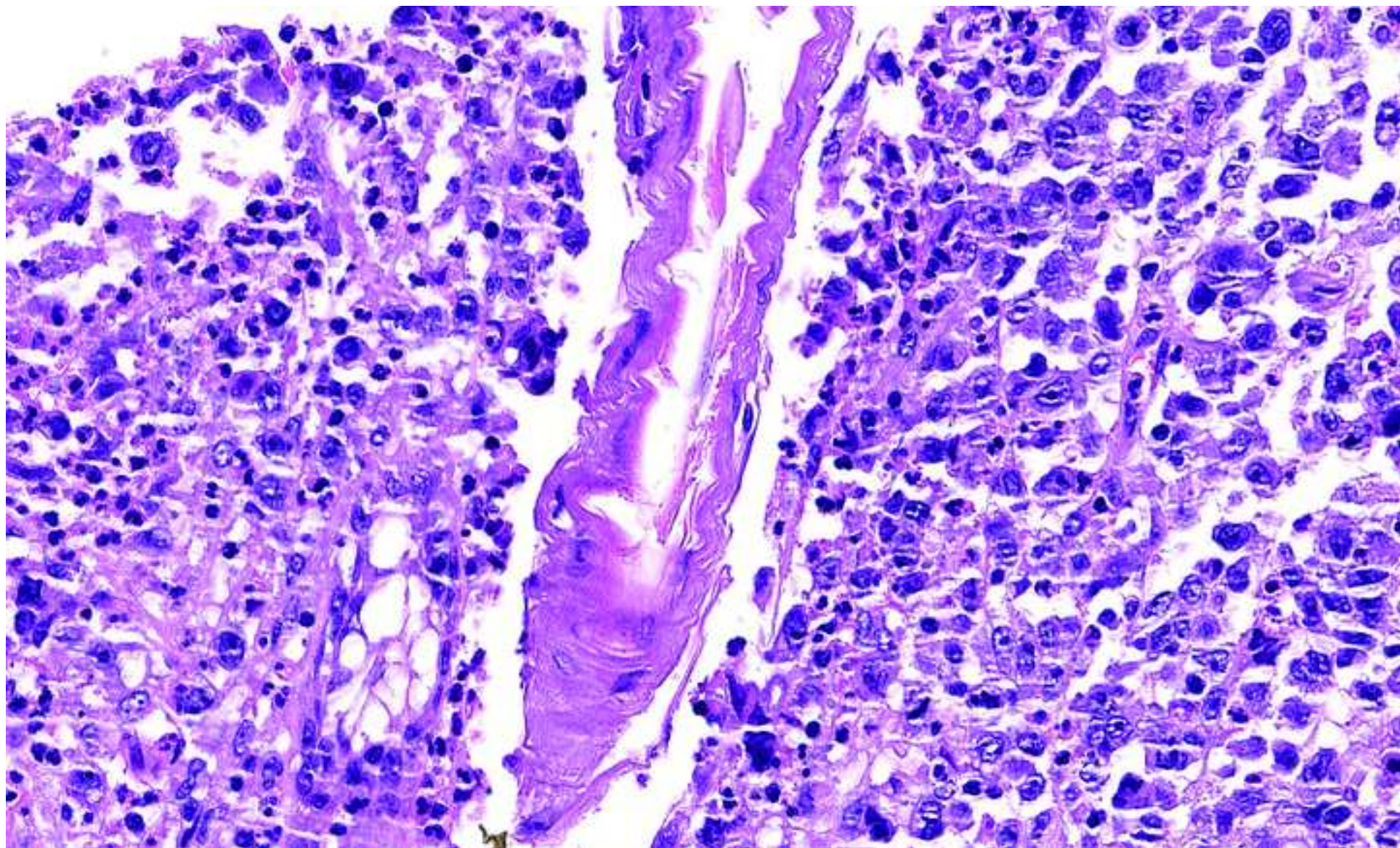


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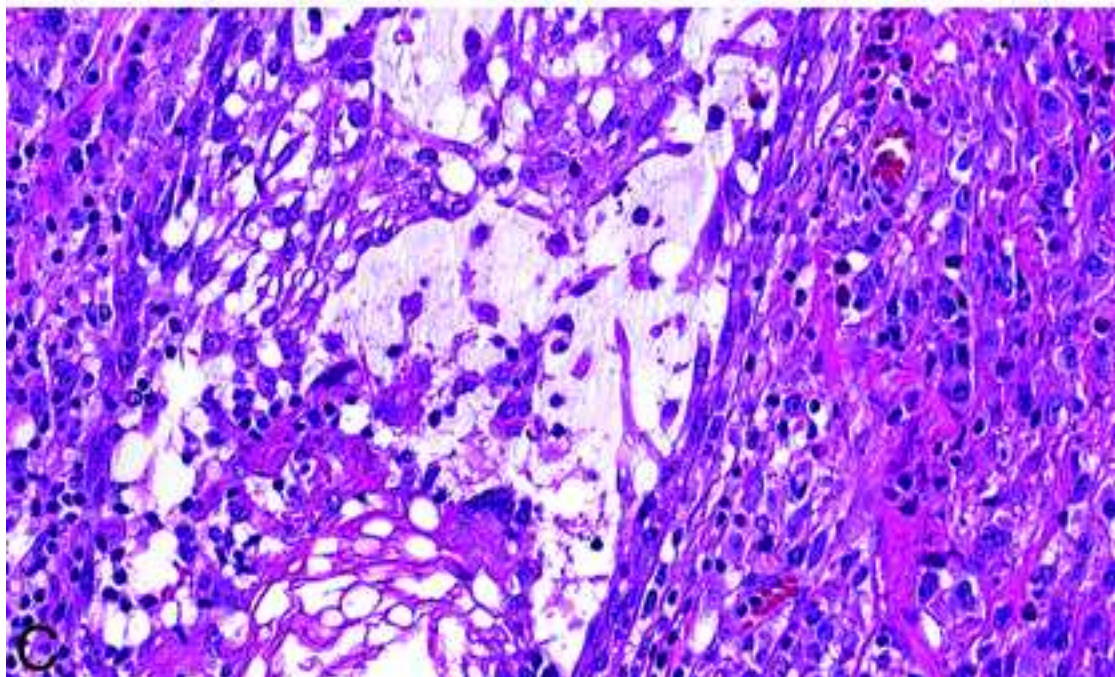
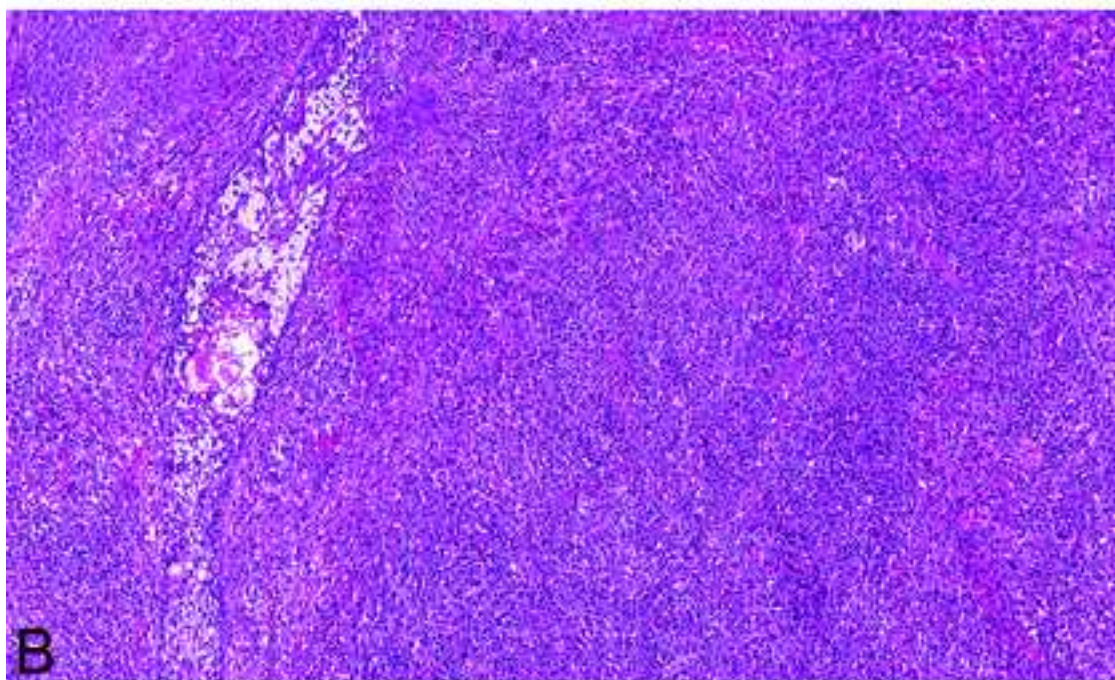
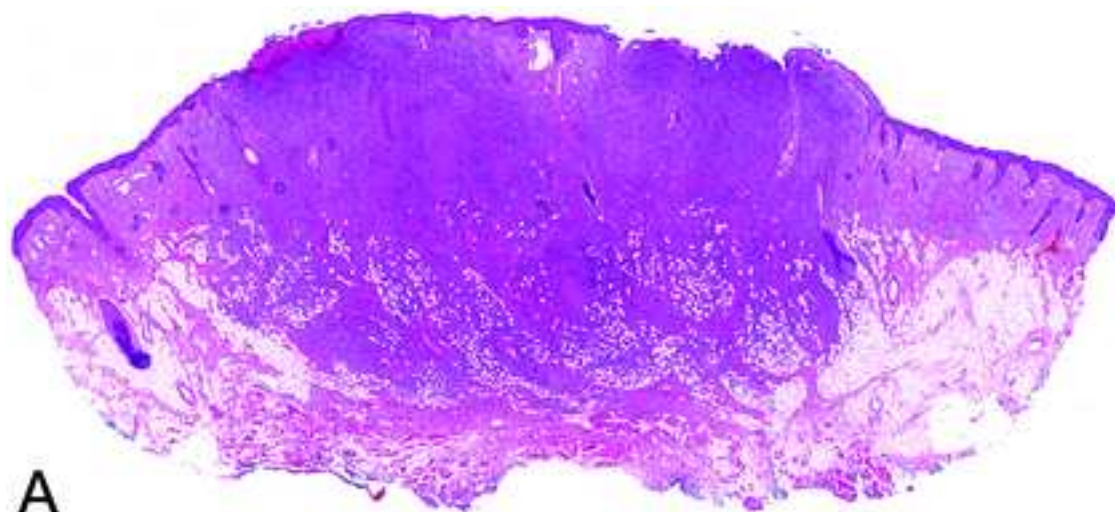


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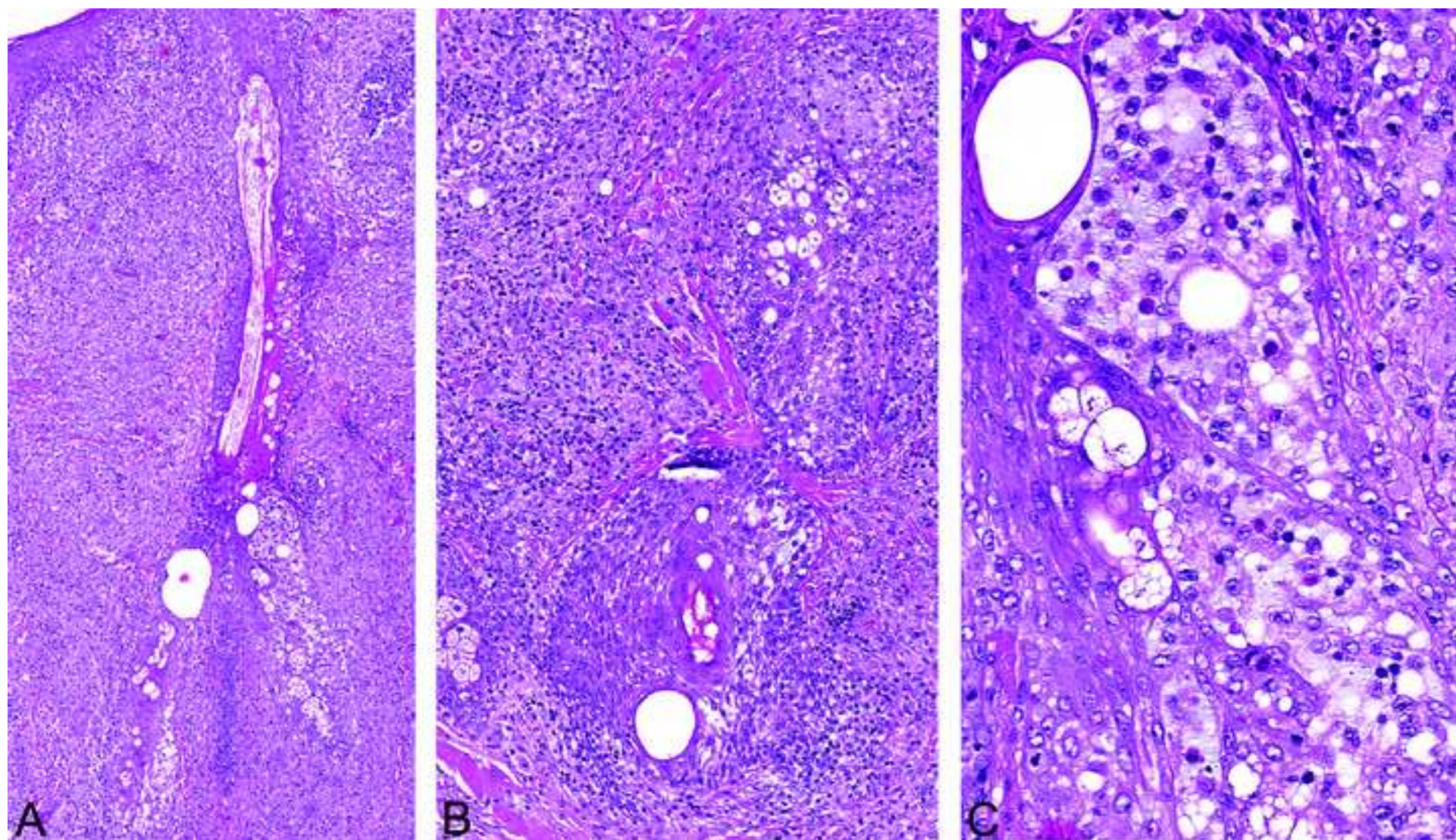
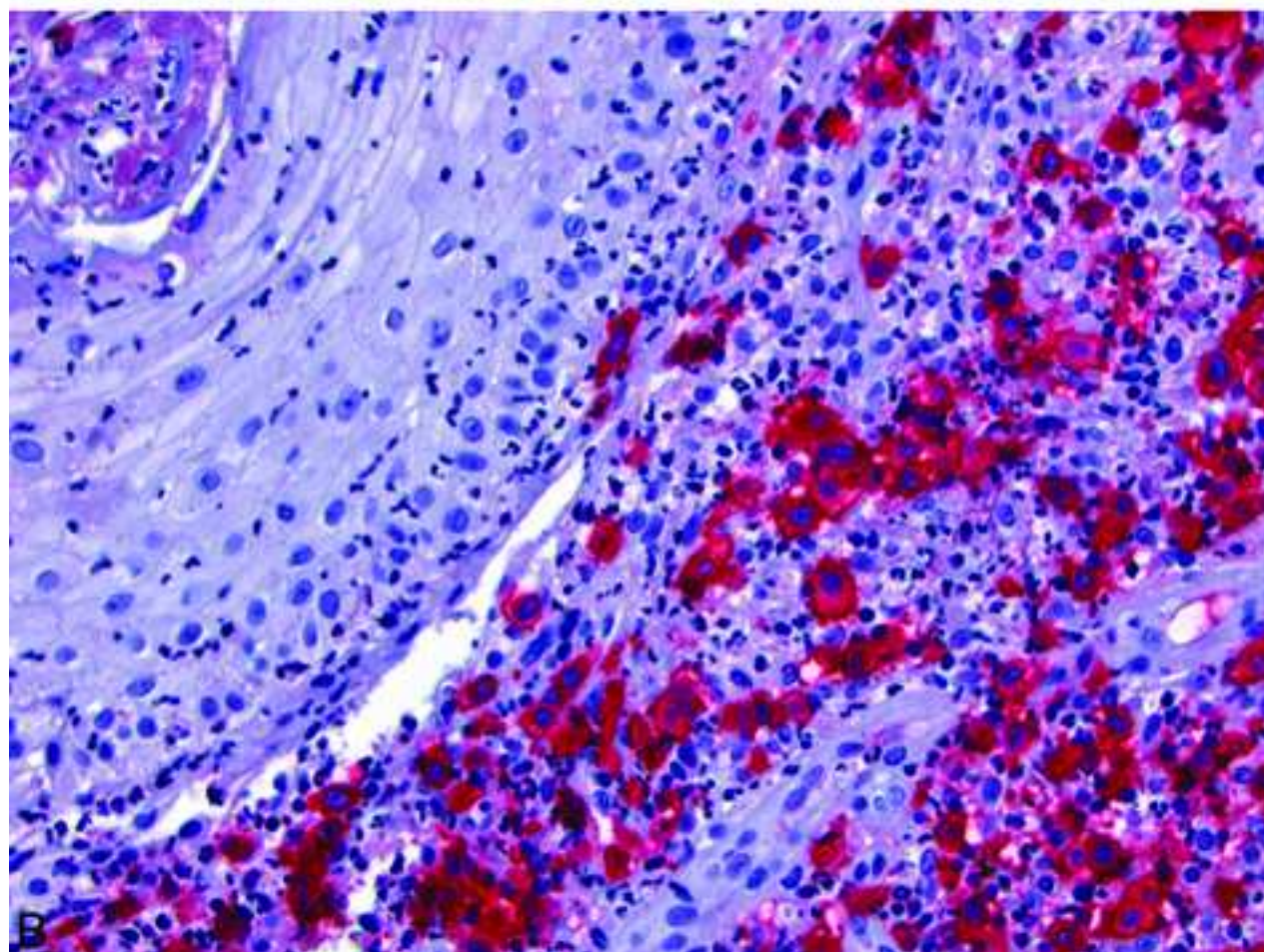
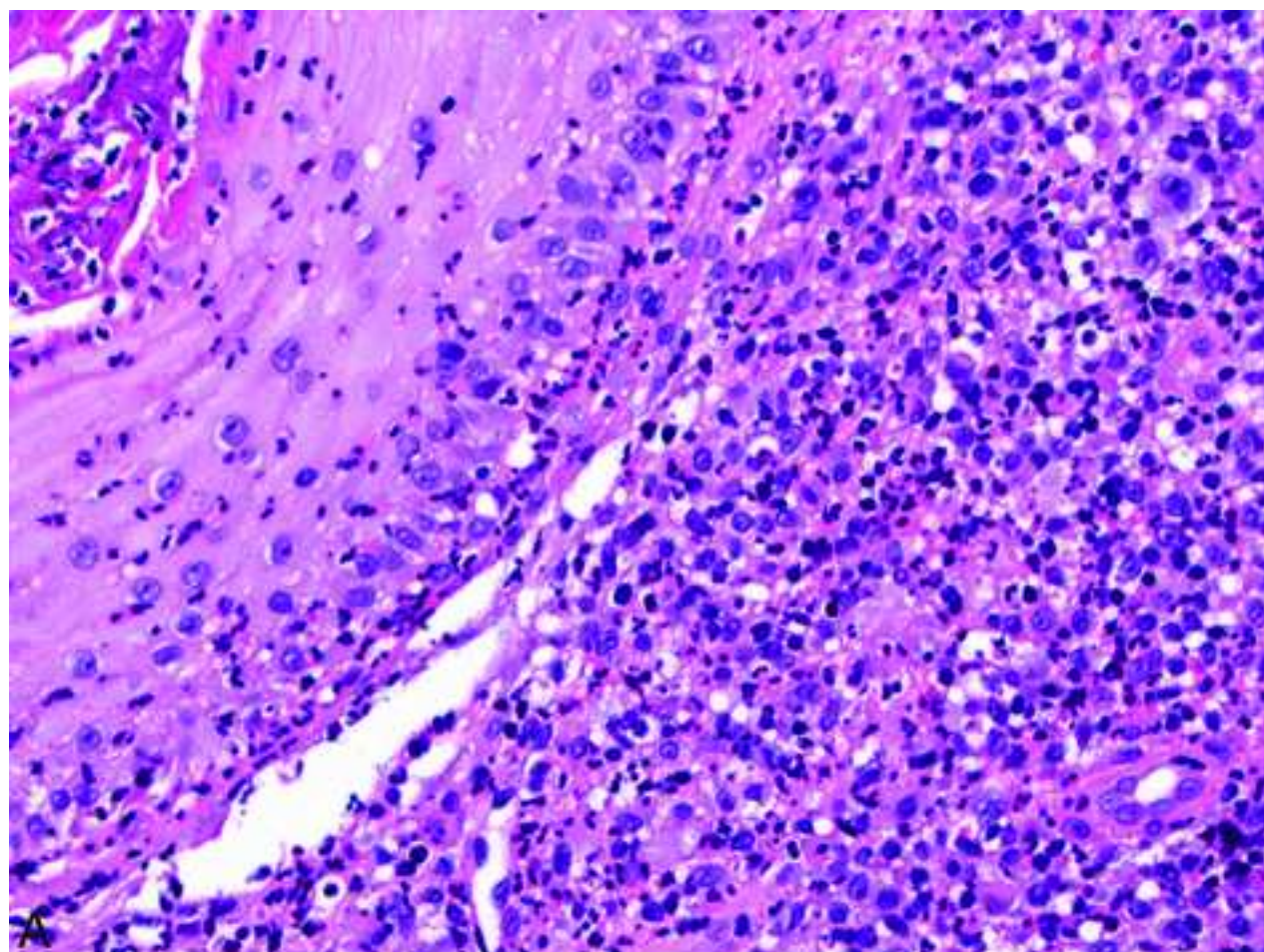
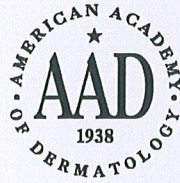


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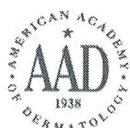
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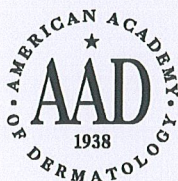
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